



## leukoencephalopathy with vanishing white matter

Leukoencephalopathy with vanishing white matter is a progressive disorder that mainly affects the brain and spinal cord (central nervous system). This disorder causes deterioration of the central nervous system's white matter, which consists of nerve fibers covered by myelin. Myelin is the fatty substance that insulates and protects nerves.

In most cases, people with leukoencephalopathy with vanishing white matter show no signs or symptoms of the disorder at birth. Affected children may have slightly delayed development of motor skills such as crawling or walking. During early childhood, most affected individuals begin to develop motor symptoms, including abnormal muscle stiffness (spasticity) and difficulty with coordinating movements (ataxia). There may also be some deterioration of mental functioning, but this is not usually as pronounced as the motor symptoms. Some affected females may have abnormal development of the ovaries (ovarian dysgenesis). Specific changes in the brain as seen using magnetic resonance imaging (MRI) are characteristic of leukoencephalopathy with vanishing white matter, and may be visible before the onset of symptoms.

While childhood onset is the most common form of leukoencephalopathy with vanishing white matter, some severe forms are apparent at birth. A severe, early-onset form seen among the Cree and Chippewayan populations of Quebec and Manitoba is called Cree leukoencephalopathy. Milder forms may not become evident until adolescence or adulthood, when behavioral or psychiatric problems may be the first signs of the disease. Some females with milder forms of leukoencephalopathy with vanishing white matter who survive to adolescence exhibit ovarian dysfunction. This variant of the disorder is called ovarioleukodystrophy.

Progression of leukoencephalopathy with vanishing white matter is generally uneven, with periods of relative stability interrupted by episodes of rapid decline. People with this disorder are particularly vulnerable to stresses such as infection, mild head trauma or other injury, or even extreme fright. These stresses may trigger the first symptoms of the condition or worsen existing symptoms, and can cause affected individuals to become lethargic or comatose.

### Frequency

The prevalence of leukoencephalopathy with vanishing white matter is unknown. Although it is a rare disorder, it is believed to be one of the most common inherited diseases that affect the white matter.

## Genetic Changes

Mutations in the *EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4*, and *EIF2B5* genes cause leukoencephalopathy with vanishing white matter.

The *EIF2B1*, *EIF2B2*, *EIF2B3*, *EIF2B4* and *EIF2B5* genes provide instructions for making the five parts (subunits) of a protein called eIF2B. The eIF2B protein helps regulate overall protein production (synthesis) in the cell by interacting with another protein, eIF2. The eIF2 protein is called an initiation factor because it is involved in starting (initiating) protein synthesis. Proper regulation of protein synthesis is vital for ensuring that the correct levels of protein are available for the cell to cope with changing conditions. For example, cells must synthesize protein much faster if they are multiplying than if they are in a resting state.

Mutations have been identified in all five of the genes from which the eIF2B protein is produced, although most of these mutations (about 65 percent) occur in the *EIF2B5* gene. These mutations cause partial loss of eIF2B function in various ways. For example, they may impair the ability of one of the protein subunits to form a complex with the others, or make it more difficult for the protein to attach to the initiation factor.

Partial loss of eIF2B function makes it more difficult for the body's cells to regulate protein synthesis and deal with changing conditions and stress. Researchers believe that cells in the white matter may be particularly affected by an abnormal response to stress, resulting in the signs and symptoms of leukoencephalopathy with vanishing white matter.

## Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

## Other Names for This Condition

- CACH syndrome
- childhood ataxia with central nervous system hypomyelination
- Cree leukoencephalopathy
- myelinosis centralis diffusa
- vanishing white matter disease
- vanishing white matter leukodystrophy

## **Diagnosis & Management**

### Genetic Testing

- Genetic Testing Registry: Leukoencephalopathy with vanishing white matter  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1858991/>

### Other Diagnosis and Management Resources

- GeneReview: Childhood Ataxia with Central Nervous System Hypomelination/  
Vanishing White Matter  
<https://www.ncbi.nlm.nih.gov/books/NBK1258>

### General Information from MedlinePlus

- Diagnostic Tests  
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy  
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling  
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care  
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation  
<https://medlineplus.gov/surgeryandrehabilitation.html>

## **Additional Information & Resources**

### MedlinePlus

- Health Topic: Leukodystrophies  
<https://medlineplus.gov/leukodystrophies.html>

### Genetic and Rare Diseases Information Center

- Leukoencephalopathy with vanishing white matter  
<https://rarediseases.info.nih.gov/diseases/231/leukoencephalopathy-with-vanishing-white-matter>

### Additional NIH Resources

- NINDS Leukodystrophy Information Page  
<https://www.ninds.nih.gov/Disorders/All-Disorders/Leukodystrophy-Information-Page>

### Educational Resources

- Disease InfoSearch: CACH Syndrome  
<http://www.diseaseinfosearch.org/CACH+Syndrome/1012>
- MalaCards: leukoencephalopathy with vanishing white matter  
[http://www.malacards.org/card/leukoencephalopathy\\_with\\_vanishing\\_white\\_matter](http://www.malacards.org/card/leukoencephalopathy_with_vanishing_white_matter)
- Orphanet: CACH syndrome  
[http://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=EN&Expert=135](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=135)

### Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD): Leukodystrophy  
<https://rarediseases.org/rare-diseases/leukodystrophy/>
- United Leukodystrophy Foundation  
<http://ulf.org/vanishing-white-matter-disease>

### GeneReviews

- Childhood Ataxia with Central Nervous System Hypomelination/Vanishing White Matter  
<https://www.ncbi.nlm.nih.gov/books/NBK1258>

### ClinicalTrials.gov

- ClinicalTrials.gov  
<https://clinicaltrials.gov/ct2/results?cond=%22leukoencephalopathy+with+vanishing+white+matter%22+OR+%22Hereditary+Central+Nervous+System+Demyelinating+Diseases%22>

### Scientific Articles on PubMed

- PubMed  
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28leukoencephalopathy+with+vanishing+white+matter%5BTIAB%5D%29+OR+%28cree+leukoencephalopathy%5BTIAB%5D%29+OR+%28cach+syndrome%5BTIAB%5D%29+OR+%28vanishing+white+matter+disease%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1440+days%22%5Bdp%5D>

### OMIM

- LEUKOENCEPHALOPATHY WITH VANISHING WHITE MATTER  
<http://omim.org/entry/603896>

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Reprinted from Genetics Home Reference:

<https://ghr.nlm.nih.gov/condition/leukoencephalopathy-with-vanishing-white-matter>

Reviewed: May 2013

Published: March 21, 2017

Lister Hill National Center for Biomedical Communications  
U.S. National Library of Medicine  
National Institutes of Health  
Department of Health & Human Services